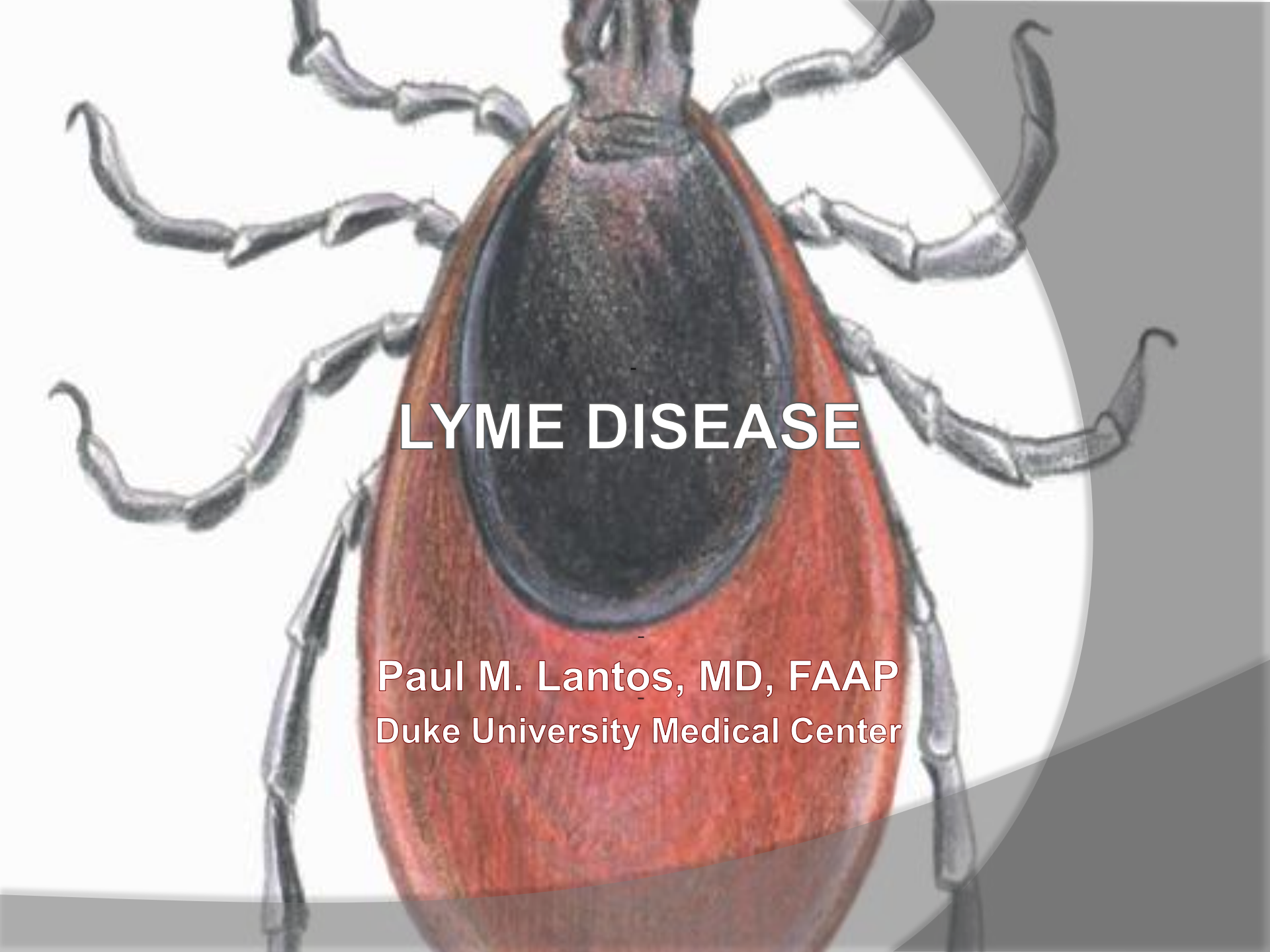

LYME DISEASE

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Disclosure

No financial relationships to disclose

Goals and Objectives

"Build a case" for the diagnosis of Lyme disease
- Epidemiologic risk, including risk in NC
- Clinical features
- Use and interpretation of lab tests

- Understand fundamentals of treatment
  - Choice of drug, route, duration
  - References to call upon
  - Complex management decisions (tick bites, doxy)

- Be familiar with the chronic Lyme controversy

Case Presentation

- 11 yo female from Wake County
- Presented to PCP in 7/09 with lethargy and a rash
  - Diffuse
  - Erythematous margins
  - “Bruised” centers
  - Warm to the touch
- Rash self-limited, lasting approximately 1 week
- Vacations in Delaware, last time > 8 months previously
- No recent travel
- Enjoys outdoor activities
- No known tick exposures

Case Presentation

3 months later

- Pain and swelling of ankle and knee
- Fever to 100.6
- Arthrocentesis: WBC 88,900 (90% PMNs)
- Synovial cultures negative
- Lyme serologies were ordered

Case presentation

- Lyme ELISA positive
- Lyme Western blot
  - IgG bands 18, 28, 30, 39, 41, 58, 66, 93
  - IgM bands 39, 41

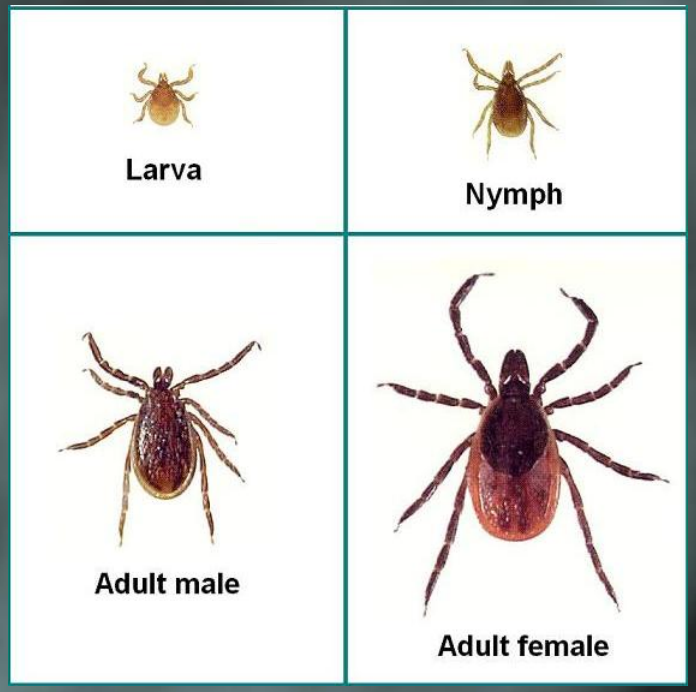
Criteria for positivity: positive or equivocal Lyme ELISA

AND

at least 5/10 IgG bands or 2/3 IgM bands

What is Lyme Disease?

- Most common vector-borne disease in North America
- Spirochete *Borrelia burgdorferi*
- Transmitted by *Ixodes* ticks
- Enzootic tick-mammal cycle
- White-footed mouse = reservoir
- Acute and subacute syndromes



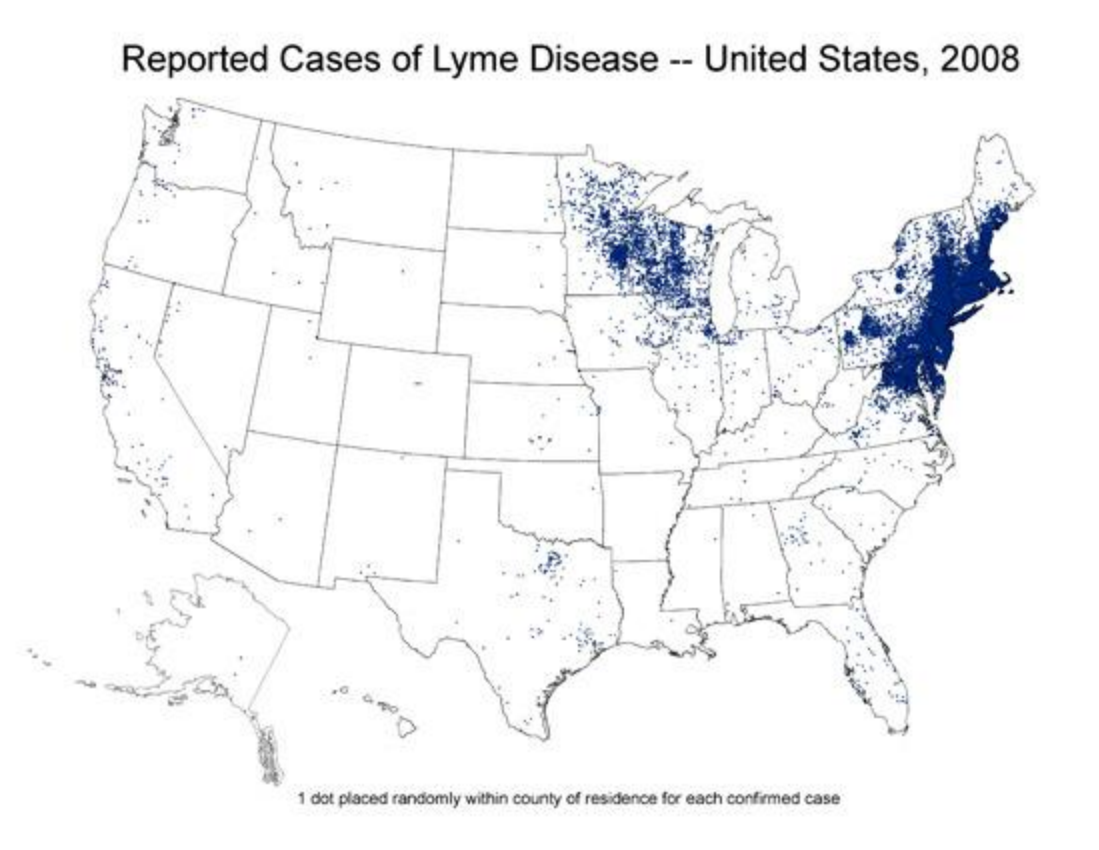
Building the Case

- Plausible exposure?
  - Time in endemic area?
  - Risky activities?
  - Tick bite?
- Plausible illness?
- Will a test help?
  - Will a negative rule it out?
  - Will a positive rule it in?

Where can you catch Lyme disease?

- 80-90% of cases in NE USA
- Most remaining cases in upper Midwest
- Low level transmission in northern California
- Most cases outside these regions are imported
- Unclear if / where / when Lyme disease will spread

Distribution

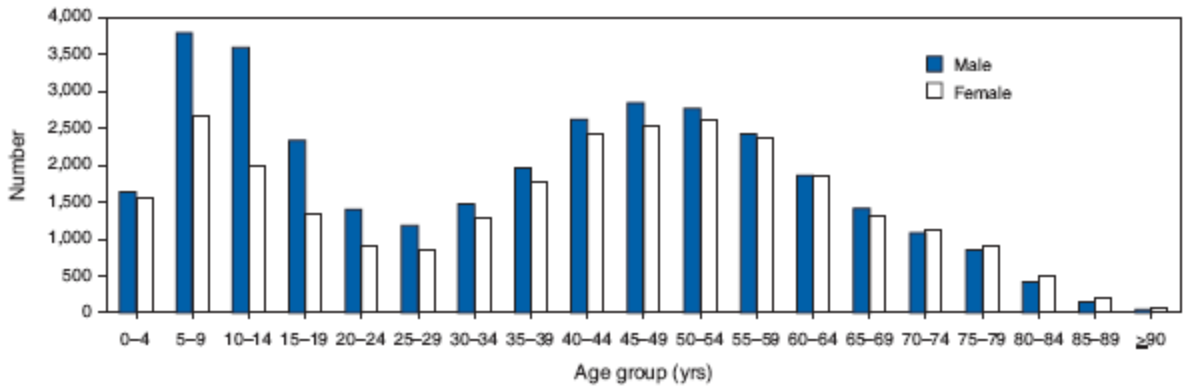


http://www.cdc.gov/ncidod/dvbid/LYME/ld_Incidence.htm

cdc.gov

Age and Gender

FIGURE 2. Number* of newly reported Lyme disease cases, by sex and age group — United States, 2003–2005



* N = 62,206.

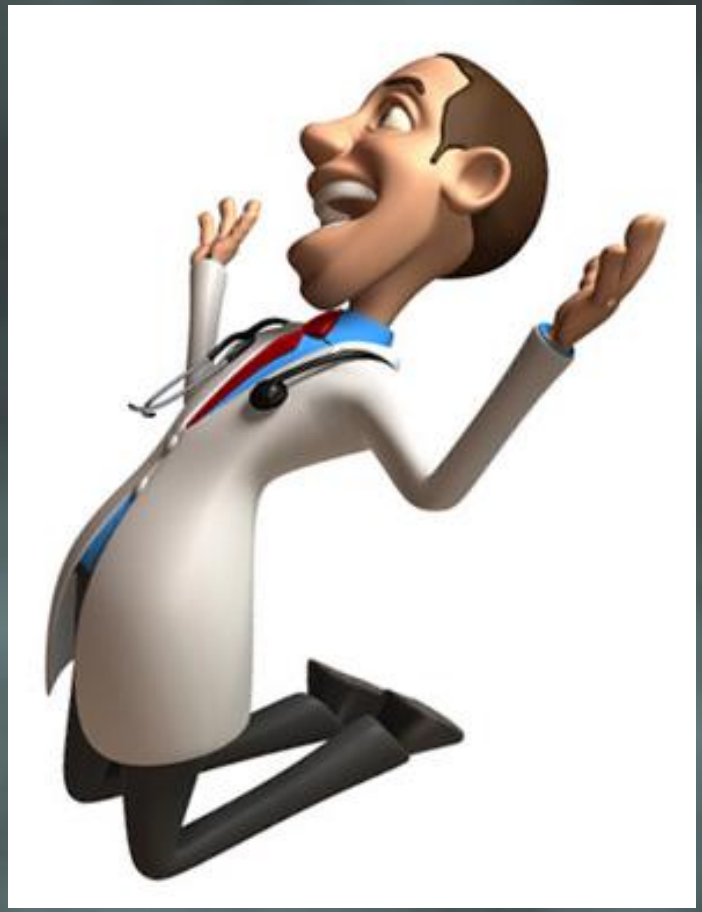
MMWR, June 15, 2007, 56(23);573-576

cdc.gov

The Case for Exposure

How Will I Recognize Lyme?

- Early localized
  - Erythema migrans (EM)
- Early disseminated
  - Disseminated EM
  - Neuroborelliosis
  - Carditis
- Late disseminated
  - Arthritis



Erythema Migrans

- Seen in 70-80% of patients
- Typically 7-14 days after tick bite
- Expanding, round, erythematous, inflammatory
- May or may not have “bullseye” appearance
- Greater than **5 cm** is more specific
- Erythema migrans is not pathognomonic


cdc.gov


www.idimages.org


www.idimages.org

Early Disseminated Lyme

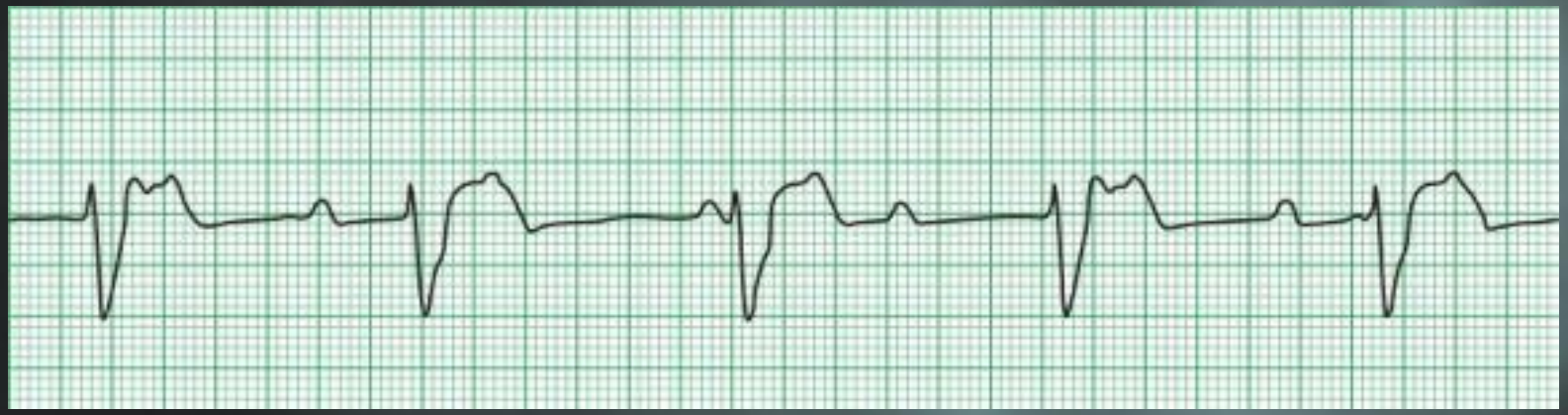
- Days-Weeks
- Multiple EM
- Constitutional symptoms
  - Malaise
  - Fatigue
  - Achiness
  - Lymphadenopathy
  - Headache

Neuroborreliosis

- 15% of untreated patients
- Weeks-months after infection
- **Meningitis**
  - Headache, meningeal symptoms
  - Lymphocytic pleocytosis
- **Cranial and peripheral neuropathies**
  - May or may not coexist with meningitis
  - 6th and 7th nerve palsies common
  - Polyradiculopathy

Lyme Carditis

- 5% of untreated patients
- Several weeks after infection
- AV block
  - May be any degree, including complete
    - Pacemakers occasionally required (temporary)
  - Usually self-limited or responds to therapy



Lyme Arthritis

- 60% of untreated patients
- Months after onset of illness
- Intermittent attacks of arthritis
  - Typically one or two large joints, esp knee
  - Swelling and stiffness, somewhat painful
  - Seldom erythematous
  - Generally less than 100,000 WBC
    - Mostly neutrophils

Antibiotic-refractory Lyme arthritis

- 10% of treated patients
- Persistent inflammation for months-years
  - Histopathology of chronic inflammatory arthritis
- Nearly always PCR and culture negative
  - Both synovial tissue and joint fluid
- HLA-DRB1-associated
- Should be regarded as *autoimmune* phenomenon

Principles of Diagnostic Testing

- **No manifestation of Lyme is pathognomonic**

- Diagnostic tests are a **decision-support** tool
  - Not equivalent to "truth"
  - Only as good as their application and interpretation

  - Transform a **pre-test** into a **post-test** probability
    - If pre-test probability low, false positives are a problem
    - If pre-test probability high, false negatives are a problem

Diagnostic Testing

- Two-step serologic test
  - ELISA
    - Whole cell *B. burgdorferi* lysate
  - Western Blot
    - IgG 10 bands – ≥ 5/10 = positive
    - IgM 3 bands – ≥ 2/3 = positive
  - ~ 40% sensitivity in erythema migrans
  - ~ 87% sensitivity in neuroborreliosis
  - ~ 97% sensitivity in Lyme arthritis

Pitfalls of Lyme Diagnosis

- Testing useful for pretest probabilities of 0.2 – 0.8
  - Testing is unnecessary for erythema migrans in endemic areas
  - More false than true positives if pretest prob < 0.2
  - 2.7 million Lyme tests in the US per year
    - False positives probably far higher than the annual incidence!
- Diagnosis of extracutaneous Lyme requires BOTH:
  - Positive serologic test
  - **Plausible clinical illness**
- IgM is not interpretable after 4-6 weeks of symptoms!
  - Pos IgM / neg IgG is a NEGATIVE test after 1-2 mo

Antibiotic options

- Doxycycline = preferred oral drug
- Beta lactam antibiotics
  - Amoxicillin
  - Cefuroxime
  - Ceftriaxone IV
  - Cefotaxime IV
- Macrolides = less effective

Principles of Therapy

- Oral therapy effective and preferred
- ALL manifestations treated in ≤ 4 weeks
- Only arthritis requires > 14 days
- For early Lyme 10 days may be effective
- Useful sources for standard treatment recs:
  - The 2006 IDSA guidelines
    - http://www.idsociety.org
  - The AAP Red Book

Difficult Treatment Issues

- Should I treat a tick bite?
  - Doxycycline (single dose) for **high risk** bites
- When should I use doxycycline in children?
  - Prohibitive beta-lactam intolerance
  - Neurologic disease
- Oral vs IV for neurologic manifestations

Chronic Lyme Disease

- **No pathologic, microbiologic, or clinical definition**
- Constitutional phenomena
  - Arthralgias, cognitive dysfunction, fatigue
- Background rate of these symptoms HIGH
  - May be no different than in “chronic Lyme” cases
- Most patients diagnosed with chronic Lyme disease lack objective evidence of infection

Efficacy of long term antibiotics

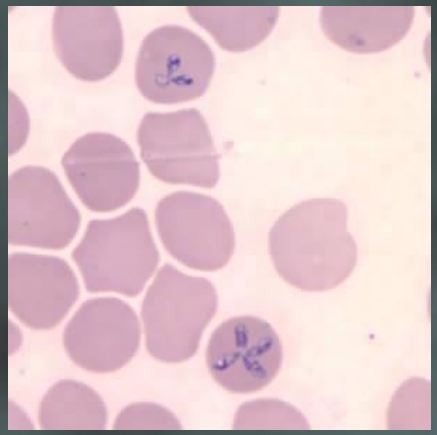
- Several major controlled clinical trials
  - Kaplan (Neurology 2003)
  - Klempner (NEJM 2001)
  - Krupp (Neurology 2003)
  - Fallon (Neurology 2007)
  - Oksi (Eur J Clin Micro Infect Dis 2007)
- Strict enrollment criteria
  - Chronic symptoms after appropriate treatment for documented Lyme
- Standardized outcome measures
  - Neuropsychological tests
  - Symptom scores
- No benefit

Evidence of Harm

- Klempner trial
  - One ceftriaxone patient had a pulmonary embolism
  - One ceftriaxone patient had fever / anemia / GI bleeding
- Krupp trial
  - Line sepsis in 3 IV placebo patients
  - Anaphylaxis in one ceftriaxone patient
- Fallon trial
  - 26% of drug (6/23) vs 7% of placebo (1/14)
  - Drug: 2 thromboses, 3 allergic rxn, 1 cholecystitis
  - IV Placebo: 1 line sepsis
- Stricker study (Minerva Med 2010)
  - 200 patients: 7 allergic reactions, 6 line sepsis, 4 DVT, 2 cholecystitis

Coinfection

- Human granulocytic anaplasmosis
  - *Anaplasma phagocytophilum*
- Babesiosis
  - *Babesia microti*



- May be transmitted in isolation or as co-pathogens
- Co-infection more severe / persistent than Lyme alone
- Suspect if high fevers, severe symptoms, abnormal labs
  - leukopenia, thrombocytopenia, anemia, electrolytes, liver enzymes

Conclusions

- Lyme may be possible in NC, but it is rare
- Lyme disease has finite, well-described manifestations
- Build a clinical and epidemiologic case before testing
- Resources and guidelines exist to assist physicians